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Longitudinal Study of Cognitive Abilities and Adaptive Behavior Levels in Fragile X Males:
A Prospective Multicenter Analysis

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Retrospective longitudinal studies have noted declines in IQ scores in many but not all fra(X) (fragile X) males and females. We report on a prospective investigation of longitudinal changes in cognitive ability (IQ) and adaptive behavior (DQ) in 24 fra(X) males from four test sites. Individuals who were tested ranged in age from 3–15 years. To determine cognitive ability, all males were administered the Stanford-Binet test (4th Edition). To assess adaptive behavior, all males were evaluated using the Vineland Adaptive Behavior Scales. Mean intertest interval was 2.3 years. Using identical DNA protocols, all subjects were identified as bearing the fra(X) mutation. Results showed declines in IQ scores in 18/24 (75%) males. Four males showed no change in scores. Declines in DQ scores were noted in 22/24 (92%) of those tested. DQ scores were higher than IQ scores in 20/24 (83%) subjects. From a descriptive cohort analysis, decreases in IQ scores appear to follow a well-defined, negatively decelerating function. Declines in DQ were steeper and more nearly linear. Declining scores are not indicative of regression of intellectual and/or social skills, but of a relative inability to keep pace with their age-normed cohort. We conclude that the fra(X) mutation affects cognitive abilities in a uniform, nonlinear manner comparable to outcomes observed in earlier retrospective studies. Adaptive behavior also declines, but in a more linear fashion.

KEY WORDS: IQ, adaptive behavior, trinucleotide repeats, mutation size, fragile X

INTRODUCTION

The fra(X) (fragile X) mutation is a principal cause of inherited mental retardation (MR). However, unlike most other individuals with MR, fra(X) children and adolescents show characteristic longitudinal changes in IQ scores. In particular, retrospective studies report that a large proportion of affected young fra(X) males [Chudley et al., 1983; Lachiewicz et al., 1987; Borghgraef et al., 1987; Prouty et al., 1988; Curfs et al., 1989, 1991; Dykens et al., 1989; Hagerman et al., 1989; Fisch et al., 1991, 1992] and fra(X) females [Hagerman and Smith, 1983; Prouty et al., 1988; Fisch et al., 1994b] show significant declines in IQ scores related to age. In addition, Dykens et al. [1993] and Fisch et al. [1994a] observed declines in adaptive behavior (DQ) scores among fra(X) male children and adolescents.

Recently, Hay [1994] raised doubts whether declining IQ scores in fra(X) individuals were a genuine phenomenon. Among other issues, Hay [1994] was concerned about problems in evaluating retrospective data, pooling results across differing IQ tests, combining outcomes from different cultural populations, and identifying cognitive deficits that may be idiosyncratic to fra(X) individuals. To correct what may have been the result of artifactual findings, Hay [1994] recommended that future studies of longitudinal changes be prospective and use a single instrument to measure cognitive ability, that tests and retests be administered at relatively fixed intervals, and that children be tested initially at several different ages. Coincidentally, we in-

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vestigated whether longitudinal declines in cognitive ability and adaptive behavior manifest themselves prospectively in fra(X) males aged 3–15 years.

MATERIALS AND METHODS

Subjects

Twenty-four English-speaking North American males between age 3–15 years diagnosed with the fra(X) full mutation were tested and retested between May, 1991–April, 1995. All subjects live at home with one or both parents. Diagnosis for the fra(X) mutation was made initially from cytogenetic evaluation and confirmed by standard DNA testing. Subjects were either probands (n = 22) or siblings (n = 2) of probands and obtained from four sites: 1) 7 were from the Greenwood Genetics Center in Greenwood, SC; 2) 7 were from the Chapman Institute in Tulsa, OK; 3) 6 were from the Ongwanada Resource Centre in Kingston, Ontario, Canada; and 4) 4 were from the Genetics and IVF Institute in Fairfax, VA.

Cognitive and Behavioral Assessment

To obtain a measure of cognitive ability (IQ score), a psychologist administered the Stanford-Binet test, 4th Edition (SBFE) [Thorndike et al., 1986]. The battery consists of a variety of subtests grouped into four major areas: verbal reasoning; abstract/visual reasoning; quantitative reasoning; and short-term memory. To obtain a measure of adaptive behavior (DQ score), one or both parents were interviewed using the Vineland Adaptive Behavior Scales (VABS) [Sparrow et al., 1984]. The VABS contains questions from four domains: communication; daily living skills; socialization; and motor skills for children under age 6 years. Both measures of IQ and DQ have demonstrated excellent reliability and validity [Sattler, 1988].

Procedure

Beginning in May 1991, 43 fra(X) males with the full mutation were tested prospectively and administered the SBFE and VABS for the first time. Initial testing of subjects extended over a period of 2 years. To date, 24 males have been retested. Mean intertest interval (ITI) was 2.3 years (±0.9 years). Eighteen males were tested and retested by one psychologist (G.S.F.); 6 subjects were tested and retested by a second psychologist (R.S.).

DNA Testing

All subjects evaluated cognitively and behaviorally were provided DNA testing at each of the four centers. Genomic DNA was extracted and digested using *Eag*I and *Eco*RI restriction enzymes. A more detailed analysis of DNA testing and analysis can be found in Fisch et al. [1996].

Data Analysis

IQ and DQ scores, as well as standardized test and retest (z) scores for the SBFE and VABS, were analyzed. In addition, standardized difference scores (Zdiff) were computed using the formula provided by Sattler [1988] and used previously by Lachiewicz et al. [1987], Hagerman et al. [1989], and Fisch et al. [1991].

RESULTS

Results showed a decline in IQ scores in 18/24 (75%) of subjects tested. Four males exhibited no change in IQ, while 2 others manifested small increases (see Fig. 1). Declines in DQ scores were observed in 22/24 (92%) of those evaluated (see Fig. 2). In 20/24 (83%) males, DQ scores were higher than IQ.

Of the subjects tested, 7/24 (29%) were methylation mosaics. Given the results obtained previously by Rousseau et al. [1994] and McConkie-Rosell et al. [1993], we compared the cognitive-behavioral and molecular-genetic features of our subgroup of methylation mosaics with those of the fully mutated males. Data are presented in Table I. Results indicate that there are no significant differences between groups in age tested or retested, or in any of the cognitive-behavioral or molecular-genetic measures examined. Although mean Zdiff IQ and Zdiff DQ scores of fully mutated males appear to be lower than those of methylated mosaics, the differences are not significant ($P > .5$). Since the results indicate no significant differences between subgroups, their data were pooled for subsequent analysis.

Originally, we intended to construct a general linear model in which the two outcome variables, Zdiff IQ scores and Zdiff DQ scores, would be characterized as functions of three predictor variables: 1) age tested; 2) initial IQ (or DQ) score; and 3) mutation size. However, age at first test and age at second test were almost perfectly correlated ($r = 0.96$; $P < .001$). Also, age at first test was strongly and significantly correlated with initial IQ score ($r = -0.78$; $P < .001$) and moderately correlated with initial DQ score ($r = -0.57$; $P < .003$).

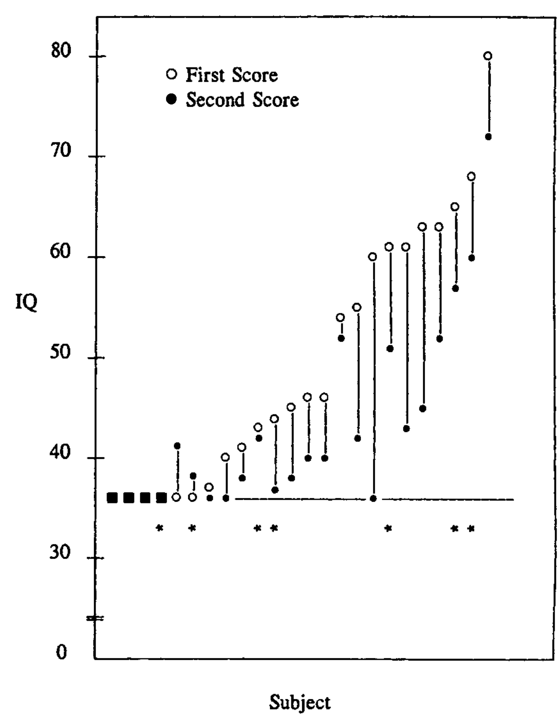

Fig. 1. Initial and retest IQ scores for young fra(X) males (n = 24). Asterisk indicates scores for methylated mosaics.

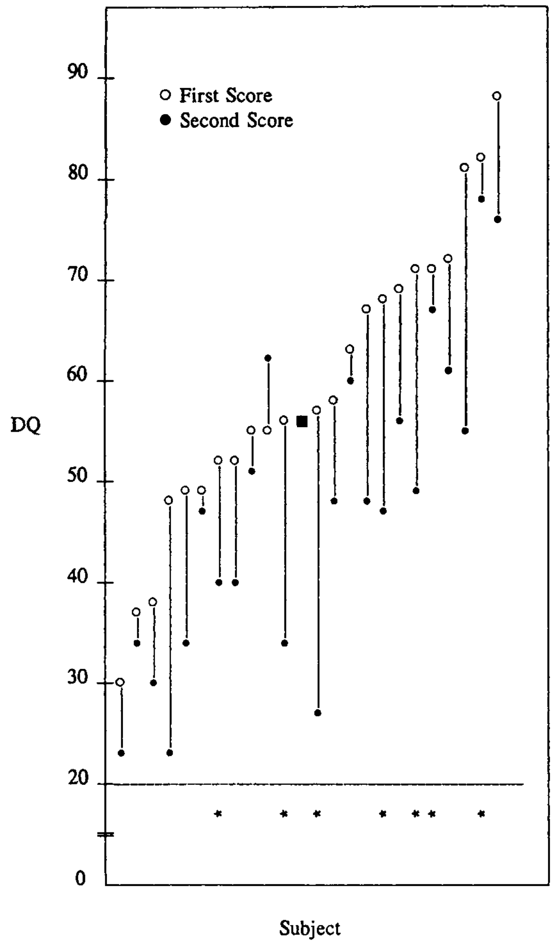

Fig. 2. Initial and retest DQ scores for young fra(X) males (n = 24). Asterisk indicates scores for methylated mosaics.

Moderate-to-high correlations among predictor variables in multiple regression analysis have a distorting effect on computation, i.e., multicollinearity. In addition, plotting change against initial value is almost certain to produce a negative correlation, since the initial IQ score appears in both variables [Campbell and Machin, 1993]. Therefore, instead of developing a general linear model to describe the relationship between Zdiff scores together with the several predictor variables, we present the correlation of Zdiff scores with each predictor separately and discuss their individual relationships.

TABLE I. Group Means of Age Tested, and Cognitive-Behavioral and Molecular-Genetic Measures, for Methylated Males (n = 7) Compared to Fully Mutated Males (n = 17) (±SD)

	Methylated males	Fully mutated males
Age first tested (months)	99 (8.3)	94 (7.8)
Age at retest (months)	123 (10)	122 (10)
First IQ score	51 (14)	49 (13)
Retest IQ score	46 (10)	42 (9)
First DQ score	63 (15)	58 (15)
Retest DQ score	49 (17)	47 (15)
Mutation size	2.0 (0.8)	1.8 (0.6)
Zdiff IQ	−1.2 (1.2)	−1.8 (2.0)
Zdiff DQ	−1.9 (1.6)	−2.1 (1.9)

Relationship Between Age First Tested With Zdiff IQ and Zdiff DQ

Examination of the data scatterplot revealed a curvilinear relationship between age first tested and Zdiff IQ score (data not shown). To linearize the relationship, we transformed age first tested by computing its natural logarithm. Results indicate that log(age) was moderately and significantly correlated with Zdiff IQ scores ($r = 0.52$; $P < .01$). A second scatterplot revealed a linear relationship between age first tested and Zdiff DQ score (data not shown). However, the computed Pearson coefficient between age first tested and Zdiff DQ score was near zero ($r = .14$; $P > .52$), indicating that the size of the difference in DQ scores from first to second assessment was unrelated to the age at which the child was tested.

Relationship Between Mean IQ (or DQ) and Zdiff IQ (or DQ)

As noted earlier, instead of computing the correlation between Zdiff IQ and initial IQ, we calculated the relation between Zdiff IQ and mean IQ [Campbell and Machin, 1993]. Results show that mean IQ score was moderately and negatively correlated with Zdiff IQ score ($r = 0.48$; $P < .02$), but mean DQ score shows no correlation with Zdiff DQ score ($r = .03$; $P > .87$).

Relationship Between Mutation Size and Zdiff IQ (or DQ)

We examine the relationship between mutation size and Zdiff IQ and Zdiff DQ. Results indicate a near zero, nonsignificant relationship between Zdiff IQ and mutation size ($r = -0.17$); $P > 0.43$), and a near zero, nonsignificant relationship between Zdiff DQ and mutation size ($r = 0.02$; $P > 0.92$). Finally, we investigated whether changes in IQ scores and changes in DQ scores were related to one another. Results indicated a near-zero, nonsignificant relationship ($r = -.07$; $P > .75$).

To delineate the effect of age tested, we examined longitudinal changes in IQ and DQ according to the age cohort in which the subjects were initially tested. For this sample, subjects were separated into three age cohorts: 1) those tested initially between age 3–<6 years (n = 9); 2) those tested initially between age 6–9 years, inclusive (n = 8); and 3) those tested initially after age 9

TABLE II. Statistically Significant Longitudinal Changes in IQ and DQ

	Significant decreases (Zdiff ≤ −1.96)	Nonsignificant changes (−1.96 < Z < 1.96)	Significant increases (Zdiff ≥ 1.96)
IQ scores	10	14	0
DQ scores	12	12	0

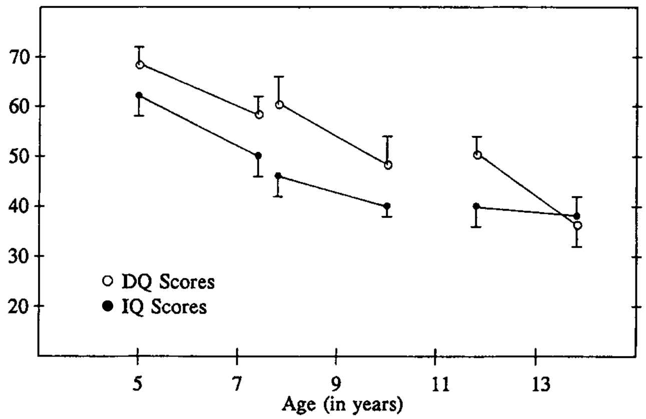

Fig. 3. Longitudinal changes in IQ and DQ scores according to age cohort in which subjects were tested initially (⊤, SEM). For cohort 1, mean age at initial testing was 5.0 years (range 3–6; n = 9); mean age at retest was 7.5 years. For cohort 2, mean age at initial testing was 7.8 years (range 6–9; n = 8); mean age at retest was 10 years. For cohort 3, mean age at initial testing was 11.9 years (range >9; n = 7); mean age at retest was 13.9 years.

years (n = 7). Results are presented in Figure 3. Note that in each cohort, both IQ scores and DQ scores decline. However, the decline in IQ scores appears to follow a negatively accelerating nonlinear curve, while the decline in DQ scores appears to be linear. Note also that DQ scores are higher than IQ scores in each cohort, but that the difference diminishes over time.

Finally, we examined whether changes in IQ and DQ scores were significantly different from the first test to the second. Therefore, Zdiff IQ and Zdiff DQ scores were separated into three categories: 1) standardized difference scores that were at most −1.96, i.e., the second IQ score was significantly lower than the first at the $\alpha = .05$ level; 2) standardized difference scores that were between −1.96–+1.96, i.e., there were no statistically significant changes in either direction; and 3) standardized difference scores that were at least +1.96, i.e., the second IQ score was significantly higher at $\alpha = .05$ level. Results are presented in Table II.

Regarding cognitive abilities, 10/24 (42%) fra(X) males showed a statistically significant decrease in IQ scores, while the remainder showed little or no change. None of those tested exhibited significant increases in IQ scores. When adaptive behavior levels were considered, 12/24 (50%) males manifested a significant decrease in DQ scores, while the remainder showed little or no change. No one tested exhibited a significant increase in DQ.

DISCUSSION

Results from our prospective multicenter study indicate clearly that declines in both IQ and DQ scores occur frequently among young fra(X) males. Our findings corroborate previous reports of cross-sectional decreases [Sutherland and Hecht, 1985; Prouty et al., 1988], as well as retrospectively demonstrated longitudinal declines in young fra(X) males with full mutations [Chudley et al., 1983; Lachiewicz et al., 1987; Borghgraef et al., 1987; Prouty et al., 1988; Curfs et al., 1989, 1991; Dykens et al., 1989; Hagerman et al., 1989; Fisch et al., 1991, 1992]. We also noted declines in methylated mosaics as well as in fully mutated males. In conjunction with the results obtained by Fisch et al. [1994b], declines in cognitive and adaptive behavior levels are likely to be observed in affected females also.

More to the point, a much larger-than-expected proportion of those who demonstrated decreases had retest scores significantly lower than their initial IQ or DQ scores. Assuming a normal distribution of test-retest difference scores, only one subject in a sample of n = 24 would be expected to exhibit a significant decline (Zdiff < −1.96) in either IQ or DQ scores. Our results indicate that 10 times as many males show significant decreases than expected probabilistically. In those instances in which little or no change occurred in test-retest IQ scores, stability could be attributed to one of two factors. Either scores were already at or near floor values permitted by the scoring guide, or subjects with the least change in scores were among the oldest in the sample, in whom IQ had already attained a natural base.

Previously, retrospective studies regarded the decline in IQ scores as a consequence of the increasingly abstract nature of the IQ test [Hagerman et al., 1989]. We noted declining DQ scores as well as declining IQ scores. Moreover, the declines were manifested in all four subscale area scores of the SBFE (verbal reasoning, visual/spatial reasoning, quantitative reasoning, and short-term memory), and in all three domains of the VABS (daily living skills, communication, and socialization). This demonstrates that the decline is broadly based and affects all dimensions of cognitive and behavioral abilities.

It should be noted that declining IQ or DQ scores do not imply regression of intellectual and/or social skills or CNS degeneration, as Fisch et al. [1992] noted previously. What appears to be the case is that cognitive and/or behavioral development "plateaus" during childhood or early adolescence, as Dykens et al. [1989, 1993] have remarked. Cognitive abilities and adaptive behaviors that have been acquired are not eradicated. While not analyzable quantitatively, we compared subjects' initial responses to subtest items to their subsequent retest responses. We found that most subjects were able to respond correctly to more items presented on retest than to items presented initially. Most subjects demonstrated a larger vocabulary, and could remember more items presented visually or longer sentences presented orally. However, they were unable to maintain the pace with which their same-age cohort increased. Consequently, their IQ and DQ scores were lower.

Declining IQ scores are not confined to young males with the fra(X) mutation. Using the Bayley Scales of Infant Development, Wishart [1993] found that the developmental rate of Down syndrome (DS) infants declined to half the normal rate. In a cross-sectional study, Cornwell and Birch [1969] noted that both IQ and DQ scores among DS children were significantly lower in older subjects. Fishler and Koch [1991] reported that even higher-functioning mosaic DS chil-

dren show declines in IQ scores. In her review of longitudinal research in DS, Carr [1992] concluded that there is a real decline in IQ score as a function of age. Ogasawara [1989] reported a downward shift in IQ among individuals with Duchenne muscular dystrophy. However, not all genetic disorders produce declining IQ scores. Dykens et al. [1992] found that adolescents and young adults with Prader-Willi syndrome show no changes in IQ.

Hay [1994] argued that the use of different instruments to retest individuals may have contributed to declines in IQ scores observed in retrospective analyses. Previous studies showed that IQ scores increased systematically when adolescents tested with the WISC or WISC-R were retested with the WAIS or WAIS-R. Walker and Gross [1970] noted an average increase of 10 points when mild-to-moderately retarded children were tested with the WISC and retested with the WAIS. Vance et al. [1987] found that adolescents with borderline IQ scores demonstrated a 5-point increase when tested with the WISC-R and retested with the WAIS-R. Decreases in IQ scores have been observed when standardized tests are renormed [Doppelt and Kaufman, 1977; Bolen et al., 1995]. On the other hand, children with cognitive deficits who were tested initially with the WISC-R and retested with the SBFE [Lukens, 1990; Hollinger and Baldwin, 1990], or who were tested with the SB-LM and retested with the WISC [Walker and Gross, 1970], or tested with the SB-LM and retested with the SBFE [Lukens, 1988], or tested with the SBFE and retested with the WISC-R [Lukens, 1990], showed no appreciable changes in IQ scores.

Since we administered the same IQ instrument at test and retest, declines in IQ score cannot be attributed to the use of different test implements. To the contrary, earlier studies have shown that testing and retesting individuals with cognitive deficits using the same IQ tests, e.g., mild-to-moderately retarded children [Walker and Gross, 1970; Silverstein, 1983], children in the juvenile court system who have low-normal IQs [Haynes and Howard, 1986], learning-disabled children with borderline-to-low-normal IQs [Haddad et al., 1984], children with borderline IQs [Naglieri and Pfeiffer, 1983], or moderately retarded adults [Watkins and Campbell, 1992], showed no differences in mean IQ scores. Except for children with Down syndrome or myotonic dystrophy, MR individuals do not typically show systematic declines in IQ scores. Therefore, results from our study indicate that the findings are robust.

Since the same psychologist administered the test to each subject, one cannot attribute changes in IQ scores to the use of different psychometricians. Given that the test was administered only to English-speaking North Americans, one cannot attribute decline in IQ scores to the use of testing among different cultures, which, as Hay [1994] also suggested, may be problematic. In summary, results from our investigation provide compelling evidence that declines in IQ scores among fra(X) males cannot be attributed to the systematic effects of differences in test instruments, differences in psychometricians, and differences in languages and/or cultures in which the test was administered, nor to any factor proposed by Hay [1994]. We conclude that declining IQ scores among fra(X) males is a valid phenomenon.

We note further that adaptive behavior levels are less impacted than cognitive abilities in all but 2 individuals tested (92%), which confirms results obtained by Fisch et al. [1994a]. Mean DQ at initial testing was 59, while mean IQ was 9 points lower. On retest, mean DQ was 48, while mean IQ was 43. This indicates that IQ scores decline less steeply than adaptive behavior levels, partly because their scores are nearer to the floor values of the test. It would also explain, in part, why younger children may appear to be less affected than older ones.

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